Office Action Summary	Application No.	Applicant(s)
	10/573,813	WADA ET AL.
	Examiner	Art Unit
	MARIA LEAVITT	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,15,16,18,19 and 41-75* is/are pending in the application.

4a) Of the above claim(s) *46-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,15,16,18,19 and 41-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.*2*(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 7, 15, 16, 18, 19, 41-75 are currently pending. Claims 7, 15, 16, 18, 19 and 41-45 have been amended by Applicants' amendment filed on 05-31-2011. Claims 46-75 were previously withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Therefore, claims 7, 15, 16, 18, 19 and 41-45 are currently under examination to which the following grounds of rejection are applicable.

Rejections withdrawn in response to Applicants' arguments or amendments

Claim Objections

In views of Applicants' arguments, objection to claims 7 and 15 have been withdrawn.

Claim Rejections - 35 USC § 101

In view of Applicants' amendment claims 7, 15, 16, 18, 19 and 41-45 to recite the limitation "isolated", rejection of claims 7, 15, 16, 18, 19 and 41-45 under 35 U.S.C. § 101 because the claimed invention is drawn to non-statutory subject matter, has been withdrawn.

Applicants' arguments are moot in view of the withdrawn rejection.

Rejections maintained in response to Applicants' arguments or amendments

The instant claims are product claims directed to an isolated microorganism comprising a NADH-dependent D-lactate dehydrogenase (ldhA) gene from *Escherichia coli (E. coli)*, wherein

both the inherent activity of the NADH-dependent D-lactate dehydrogenase (ldhA) and the inherent activity of a pyruvate formate-lyase (pfl) in said isolated microorganism are inactivated or decreased, wherein said microorganism activity is enhanced. The examiner has interpreted the enhanced activity of the microorganism to be enhanced NADH-dependent D-lactate dehydrogenase activity from *E. coli.*

Claim Rejections - 35 USC § 103

Claims 7, 15, 16, 18, 42 and 44 remain rejected under 35 USC 103 as being unpatentable over Zhou et al., (Jan. 2003, Applied and Environmental Microbiology, pp. 399-407) in view of Yang et al., (1999, Metabolic Engineering, pp. 141-152), and further in view of Shaw et al., (1975, J. Bacteriology, pp. 1047-1975).

Zhou et al., discloses metabolically engineered of *E. coli* (i.e., W3110) characterized in that they produce D-lactic acid. Specifically, Zhou teaches genetically engineers *E. coli* wherein the activity of pyruvate formate-lyase (*pfl)* inherent in *E. coli* is inactivated by mutation of the *pflB* gene (page 400, col. 2, paragraph 2), said mutation reducing the catabolism of pyruvate to formate (page, 401, Fig. 1). This single mutation also eliminates the production of formate, ethanol and acetate in tube cultures containing 1% glucose (p. 402, col. 2). W3110 SZ32 mutant strain having a deleted *pfl* (Δ pfl) exhibits increased production of D-lactic acid in relation to parental strain W3110, e.g. 49.23±1.26 vs. 30.69 ±2.49, respectively (page 402, Table 2). Additionally, Zhou et al., generates other W3110 mutants wherein competing pathways for the production of D-lactate were eliminated including mutations for genes encoding for alcohol /aldehyde dehydrogenase (*adhE*) which eliminates or reduces ethanol production and acetate kinase (*ackA*) which eliminates or reduces acetate production, e.g., SZ63 (*pflB frd adlhE ackA*)

(p. 403, table 3; Abstract). Fermentation of mutants *E. coli* W3110 in 5% glucose produced significant improvement in the production and purity of D-lactic acid. Note that glycolysis terminates when pyruvate is reduced via NADH and H+ to D-lactate (e.g., in the presence of lactate dehydrogenase, e.g. *ldh;* Fig. 1, page 2003), or in the presence of alcohol dehydrogenase to ethanol, or in the presence of pyruvate formate lyase (*pfl*) to formate, or in the presence of pta-ackA to acetate, (page 401, col. 2, last paragraph; Fig. 1; p.2003)(**Current claims 7, 16, 42, and 44 in part**).

Zhou et al., does not specifically teach a metabolic engineering *E. Coli* with reduced activity in a FAD-dependent D- lactate dehydrogenase (*dld*) which catalyzes mainly the reverse reaction from D-lactic acid to pyruvic acid .

However, at the time the invention was made, Yang discloses that *E. Coli* expresses three types of lactate dehydrogenase: two are membrane bound NAD-independent LDHs which irreversibly convert D- and L-lactate to pyruvate, and the third which is a fermentative NAD-linked D-lactate specific enzyme, LDH which is encoded by the *ldhA* gene induced by anaerobiosis and acidity (p. 144; third full paragraph). Yang et al., illustrated the central anaerobic metabolic pathway of *E. coli* at page 142, Fig. 1. Further Yang studies perturbation of existing pathways on the redistribution of carbon fluxes in *E. Coli* mutants including overexpression of fermentative lactate dehydrogenase (LDH) which catalyzes the production of lactate by transforming *E. coli* with a plasmid overexpressing the NADH-dependent D-lactate dehydrogenase (ldhA) gene and generation of the double mutant *E. Coli* strain YBS132 (*ackA-pta-ldhA-*). Yang teaches that LDH activities of strains carrying plasmid pTY2 showed a higher LDH activity, e.g., 25.1, vs. control values of 0.63 (p. 143, col. 1, paragraph 1; table 3); however,

the acetate level was higher than that for the control plasmid. The amount of lactate produced by *E. Coli* strain YBS132 (*ackA-pta-ldhA*-) plus the *ldhA* plasmid was 6.91 in relation to parental production of strain YBS132 (*ackA-pta-ldhA*-) (page 147, Table 5), clearly indicating that lactate productivity is improved by addition of the plasmid encoding the *ldhA* gene in an *ackA-pta-ldhA-E. Coli* strain mutant by redirecting the pyruvate flux to increase NADH-dependent D-lactate production. (**Current claims 7, 15, 16 and 18, in part**).

Shaw et al., complements the combined disclosure of Zhou and Yang by teaching double mutants *Escherichia coli* strains JS150 and JS151 lacking membrane bound flavoproteins lactate dehydrogenases L- and D-lactate dehydrogenases (e.g., catalyze the reverse reaction from D-lactic acid and L-lactic acid to pyruvic acid). Shaw et al., discloses in Table 2, that L- and D-lactate dehydrogenases are differentially expressed in *E. coli* strains. **(Current claims 7 and 16, in part**).

Therefore, in view of the benefits of metabolic engineering an *E. Coli* for production of D-lactic acid based on the generation of a mutant *E. Coli* wherein the activity of pyruvate formate-lyase (*pfl*) inherent in the microorganism is inactivated as taught by Zhou which reduces the competitive competing pathways for the production of D-lactate, in part, by reducing pyruvate metabolism to formate, it would have been *prima facie* obvious to one of ordinary skill in the art in an attempt to further enhance production of D-lactic acid to activate or mutate other genes competing at the various pathways confluent at the pyruvate node responsible for metabolizing pyruvate into D-lactic acid including overexpressing NADH-dependent D-lactate dehydrogenase (*ldhA*) gene as taught by Yang in combination with a mutant *pfl* , particularly because Zhou et al., discloses that the distribution of carbon in the fermentation of glucose to

produce organic acids, ethanol, CO_2 and H_2 is largely determined by the relative *in vivo* activities of D-lactate dehydrogenase (*ldhA* gene), pyruvate formatelyase (*pfl* gene), and phosphoenolpyruvate carboxylase (*ppc* gene)" (page 401, col. 2, last paragraph)", and a person with ordinary skill has good reason to pursue the known options within her or his grasp. Though metabolic engineering is a complex science, there are well-established protocols for genetic manipulation, and large physiological knowledge of fermentative pathways in *E. coli* for which genomic information is abundant for the production of D-lactate. Moreover, it would have been *prima facie* obvious in an attempt to provide enhanced production of D-lactic acid, to metabolically engineered E. *coli* to study how the balance flux from pyruvic acid to lactate is modified (e.g., reduced or enhanced) by: (i) each L- and D-lactate dehydrogenases membrane-bound flavoproteins which essentially catalyze the reverse reaction from D-lactic acid and L-lactic acid to pyruvic acid as taught by Shaw et al., and (ii) the fermentative NADH-dependent D-lactate dehydrogenase disclosed by Yang, particularly because the cumulative effect of each of the three types of lactate dehydrogenases may be negative, additive or synergistic in the flux of pyruvate to lactate and gene disruption and/or gene recombination in *E. coli* are relatively easy to perform. Additionally, a person with ordinary skills has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense."M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-

saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)." When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06.

Reply to applicants' arguments as they relate to rejection of claims 7, 15, 16, 18, 42 and 44 under 35 USC § 103

At page 14-17 of Applicants' response filed on 05-31-2011, Applicants essentially argue that : 1) though Zhou describes an *E. coli* mutant having a deleted *pfl* which exhibits increased production of D-lactic acid in relation to parental strain, and Yang teaches that increased LDH activities of *E. coli* strains carrying the *ldhA* plasmid produced higher D-lactic acid relative to control strain, in part by elimination of competing pathways for the production of D-lactate and metabolizing pyruvate to D-lactic acid, there is not sufficient reason to combine the teachings of Zhou and Yang as a whole, because Yang itself indicates that the Examiner's assertions are not scientifically-sound by stating:

> "Overexpression of LDH was expected to increase the competitiveness of the lactate branch and might be able to divert flux away from the acetate synthesis pathway at the pyruvate branch point similar to the heterologous expression of *B. subtilis acetolactate* synthase (Yang et al., 1999). However, the acetate level is actually higher for both GJT001 (pTY11) and GJT001(pTY2), which have LDH activities 6 to 8 times higher than that with the control plasmid" ,and at page 146,

2) Had there been certainty or predictability, the whole stated purpose of Yang - "several strains were constructed to investigate the competitiveness of various pathways at the pyruvate node. Specifically, the effects of LDH enzymatic activity on the metabolic patterns were examined"- would have been unnecessary, 3) Yang, at page 142, highlights the complexity and absolute unpredictability by stating " The positive amplification factors for all three branches possibly can

be explained by the highly complicated regulatory behaviors of the PFL branch. (Yang, Page 150), 3) Yang et al., acknowledges that the interactions are "complex" and "highly complicated" and the effect of manipulating metabolic fermentative pathways still unclear, 4) Shaw does not cure the deficiencies of Zhou and Yang by disclosing *E. coli* lacking both membrane bound L- and D-lactate dehydrogenase", 5) Shaw et al., , published 24 years before Yang, does not distinguish FAD-dependent D-lactate dehydrogenase from NADH-dependent lactate dehydrogenase, and 6) Shaw et al., teaches away from the instant invention by teaching *Escherichia coli* strains lacking membrane bound flavoproteins lactate dehydrogenases L- and D-lactate dehydrogenases. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1, 2) and 3), though metabolic engineering is a complex science, there are well-established protocols for genetic manipulation, and large physiological knowledge of fermentative pathways in *E. coli* for which genomic information is abundant for the production of D-lactate, as acknowledged by Applicants at page 3, line 1-20 of the specification as filed. The instant claims are product claims. All what is required in the claimed invention is the structure of the isolated microorganism, e.g. inactivation of inherent dld activity, inactivation of inherent pfl activity, presence of an *E. coli* ldhA wherein the *E. coli* ldhA activity is increased. There is not recitation of the intended use of the claimed isolated microorganism. Applicants have not provided an example of a structural limitation that was not address by the combined disclosures of Zhou et al., Yang et al., and Shaw et al., .The fact that overexpression of lactate dehydrogenase (ldhA) with an increase of 10 times more in the LDH activity fails to divert a large fraction of the carbon flux to lactate probably by activation of the pyruvate formate lyase

(PFL) , which leads to formation of formate and acetyl-CoA as disclosed by Yang is not dispute.

However, Yang also discloses that:

> "Under anaerobic conditions, competition for pyruvate between the branch point enzymes pyruvate formate lyase (PFL Km=2mM) and fermentative lactate dehydrogenase (LDH, Km=7.2mM) determines the partition carbon flux ..... Subsequently, the flux amplification factors (or deviation indices which can be related to the flux control coefficients) are positive for all three fluxes occur ring at the pyruvate node" (Abstract) [emphasis added]

Note that the *E. coli* mutant over- expressing LDH of Yang does not have other genes mutated and clearly exhibits a higher LDH activity, e.g., 25.1, vs. control values of 0.63 (p. 143, col. 1, paragraph 1; table 3). Also note that both the *E. coli* mutant over- expressing LDH and *E. coli ackA, pta,* and *ldhA* mutant of Yang represent mutations of genes affecting the pyruvate node represented by the branch point between lactate dehydrogenase (LDH), which catalyzes the formation of lactate, and pyruvate formate lyase (PFL), which leads to the formation of formate and acetyl-CoA, under anaerobic conditions (Yang et al., p. 142, col. 2; Fig. 1). In view of the disclosure of the metabolic relevance of the pyruvate node, easy of manipulation of *E coli* as recombinant host, knowledge of intracellular metabolic fluxes in *E. coli* that can be calculated by metabolic flux analysis to estimate flux distributions to achieve maximum yield of D-lactic acid, those of skilled in the art could readily determine what genes affecting the pyruvate node could be metabolically engineered to disrupt, block or inactivate one or more metabolic pathways in the central fermentation metabolism in *E. coli* that draw carbon away from pyruvate. For example, formate can typically be synthesized directly from pyruvate, and by inactivating the enzyme involved in the synthesis of formate, i.e. *pfl*, lactate production can be expected to increase. The level of skill and knowledge in the art is such that one of ordinary skill in the art

could design protocols for genetic manipulation in fermentative pathways in *E. coli* for the production of D-D-lactate. Indeed the specification as filed provides information regarding various functional and metabolically engineered *E. coli* mutants in their production of lactic acid. For example, FIG. 1 is a graph showing the time course of an amount of D-lactic acid accumulated in the culture solution by MG1655ΔpflΔdld/pGAPldhA strain and MG1655ΔpflΔdld/ GAPpldh genome-inserted strain as related to MG1655ΔpflΔdld strain wherein insertion of the GAPpldh genome appears to enhance production of D-lactic acid after 20 hr incubation as related to MG1655ΔpflΔdld/pGAPldhA strain and MG1655ΔpflΔdld strain (paragraph [0087] of the published application]). Thus decreased activity of an *E. coli* by mutating or reducing *pfl and dld* activities, and enhanced activity of *dhA* are limited known manipulations involved in alternate pathways interfering with central metabolism of lactate from pyruvate, absent evidence of unexpected properties of the recombinant strain such as reduced production of pyruvic acid while maintaining high productivity of D-lactic acid.

Reading 4), 5) and 6), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 SPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Shaw et al., complements the combined disclosure of Zhou and Yang by teaching double mutants *Escherichia coli* strains JS150 and JS151 lacking membrane bound flavoproteins L- and D-lactate dehydrogenases (e.g., catalyze the reverse reaction from D-lactic acid and L-lactic acid to pyruvate). Shaw et al., discloses in Table 2, that membrane bound flavoproteins L- and D-lactate dehydrogenases are differentially expressed in *E. coli* strains leading to differences in their

abilities to oxidate D- and L-lactate. Note that L- and D-flavoproteins catalyze the oxidation of D-lactate to pyruvate (Bunch et al., 1997; Microbiology, pp. 187-195; p. 187, col. 2; of record IDS filed 03/28/2006). The teachings of Zhou et al., Yang et al., and Shaw et al., are in the field of Applicants' endeavor, namely, metabolically engineered *E. coli* by reorienting central fermentation metabolism. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. Id. at ___, 82 USPQ2d at 1396.

Claims 41, 43 and 45 remain rejected under 35 USC 103 as being unpatentable over Zhou et al., (Jan. 2003, Applied and Environmental Microbiology, pp. 399-407, or record) in view of Yang et al., (1999, Metabolic Engineering, pp. 141-152 , of record) and Shaw et al., (1975, J. Bacteriology, pp. 1047-1975) as applied to claims 7, 15, 16, 18, 42 and 44 above, and further in view of Courtright et al., (*J Bacteriol.* 1970, pp. 722–728, of record).

Reply to applicants' arguments as they relate to rejection of claims 41, 43 and 45 under 35 USC § 103

At pages 17 and 18 of Applicants' response filed on 05-31-2011, Applicants essentially argue that : 1) Courtright et al., teachings are related to mutants isolated from *E. Coli* K-12 who are devoid of malate dehydrogenase activity, 2) Courtright et al., is silent about claims 41 and 43.

The above arguments have been fully considered but deemed unpersuasive.

Regarding 1) and 2), Courtright et al., complements the teachings of Zhou, Yang and Shaw by disclosing isolated malate dehydrogenase (*mdh*) E. coli mutants that do not require succinate for anaerobic growth on glucose (e.g., there is not activity from oxaloacetate to malic acid under anaerobic conditions). Mutants devoid of malate dehydrogenase activity activate the pathway leading to succinic acid via aspartic acid from oxalacetic acid. As malate is preferentially synthesized directly from OAA, those of skilled in the art could readily determine that by inhibiting *mdh* the production of lactate should be reasonably expected to be enhanced, in part by reducing competitive flux in central fermentation metabolism in E. coli. Note that the instant claims are product claims which do not place any limitation on the intended use such as high levels of production of D-lactate with concomitant reduction of pyruvic acid, for example, as disclosed at page 43, Table 7 of the specification as filed.

Claim 18 and 19 remain rejected under 35 USC 103 as being unpatentable over Zhou et al., (Jan. 2003, Applied and Environmental Microbiology, pp. 399-407, or record) in view of Yang et al., (1999, Metabolic Engineering, pp. 141-152 , of record) and Shaw et al., (1975, J. Bacteriology, pp. 1047-1975) as applied to claims 7, 15, 16, 18, 42 and 44 above, and further in view of Maier et al (US Patent Application No. 10/620487, Date of filing July 16, 2003)

Reply to applicants' arguments as they relate to rejection of claims 18 and 19 under 35 USC § 103

At pages 19 and 20 of Applicants' response filed on 05-31-2011, Applicants essentially argue that by teaching use of a promoter, Maier et al., does not remove the complexity of the art associated with Applicant' invention. Such is not persuasive.

Maier et al., complements the teachings of Zhou, Yang and Shaw by disclosing genetically engineered microorganisms including transformant *Escherichia coli* (page 2, paragraph [0026]) comprising plasmid vectors for overexpression of a yfiK target gene product under the control of the constitutive GAPDH promoter of the gapA gene. The type of gene delivered is irrelevant to control sequence used as promoter. Thus there is no reason why the GAPDH promoter of the gapA gene controlling yfiK gene expression in *E. coli* could not be expected to regulate ldhA gene expression in an isolated microorganism comprising a NADH-dependent ldhA gene from *E. coli* as easily as in *E. coli*, as *E. coli* is a subgenus of an isolated microorganism.

Claim Rejections - 35 USC § 112- Second Paragraph

Claims 7, 15, 16, 18, 19 and 41-45 remain rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is vague and indefinite in its recitation at line 6 of "and wherein said microorganism' activity is enhanced" as it is unclear as to "the activity" or activities that are intended as being encompassed by the noted phrase. Proteins are known in the prior art to have numerous activities, both specific and general. For example, all proteins of a sufficient length are known to have the activity of eliciting an antibody or immune response. It is suggested that applicant clarify the intended meaning of the noted phrase.

Claims 15, 16, 18, 19 and 41-45 are indefinite insofar as they depend from claim 7.

For the purpose of a compact prosecution the enhanced activity of the microorganism recited in claim 1 has been interpreted as enhanced E. coli NADH-dependent D-lactate dehydrogenase activity.

Conclusion

Claims 7, 15, 16, 18, 19 and 41-45 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633